UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/774,526	02/22/2013	Serengulam V. Govindan	IMMU-0031US2	7799

37013 7590 04/26/2017

Rossi, Kimms & McDowell LLP
20609 Gordon Park Square
Suite 150
Ashburn, VA 20147

EXAMINER
MOSELEY II, NELSON B

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
04/26/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mail@rkmllp.com
EOfficeAction@rkmllp.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SERENGULAM V. GOVINDAN
and DAVID M. GOLDENBERG[1]

Appeal 2017-004473
Application 13/774,526
Technology Center 1600

Before MELANIE L. McCOLLUM, ULRIKE W. JENKS, and DAVID COTTA, *Administrative Patent Judges*.

McCOLLUM, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an autoimmune disease treatment method. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The Specification "concerns compositions and methods of use of immunoconjugates, comprising one or more camptothecin moieties attached to an anti-CD22 antibody or antigen-binding fragment thereof" (Spec. ¶ 3).

---

[1] Appellants identify the real party in interest as Immunomedics, Inc. (App. Br. 2).

The Specification discloses that, "[p]referably, the anti-CD22 antibody is epratuzumab [(also known as hLL2)] and the camptothecin is SN-38" (*id.* ¶¶ 3 & 25). The Specification also discloses that the "immunoconjugate is of use to treat B cell diseases, such as . . . autoimmune disease," and that "[i]mmune diseases may include . . . systemic lupus erythematosus (SLE)" (*id.* ¶¶ 3 & 197).

Claims 1, 2, 5–10, 15, 16, 18–30, 33, 36, 37, and 39–46 are on appeal (App. Br. 3 & 16–18).[2] Claim 1 is representative and reads as follows:

1. A method of treating an autoimmune disease comprising administering to an individual with an autoimmune disease that is mediated by CD22-expressing B cells, an immunoconjugate consisting of (i) an anti-CD22 antibody or antigen binding fragment thereof; and (ii) at least one therapeutic agent attached by a linker to the anti-CD22 antibody or fragment thereof, wherein the therapeutic agent is a camptothecin.

Claims 1, 5–8, 15, 16, 18, 19, 22, 23, 29, 33, 36, 37, 39, 40, 43, and 44 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg[3] in view of Abrams[4] and Allen[5] (Final Act.[6] 3).

Claims 2 and 30 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg in view of Abrams, Allen, and Leung[7] (*id.*).

---

[2] Claims 3, 4, 31, and 32 are also pending but have been withdrawn from consideration (11/5/15 Amend. 2 & 6 & 3/27/2014 Final Act. 1).
[3] Goldenberg et al., WO 00/74718 A1, Dec. 14, 2000.
[4] Abrams, US 4,867,962, Sep. 19, 1989.
[5] Allen et al., US 6,056,973, May 2, 2000.
[6] "Final Act." refers to the Final Office Action dated May 5, 2015.
[7] Shui-on Leung et al., *Construction and Characterization of a Humanized, Internalizing, B-cell (CD22)-Specific, Leukemia/Lymphoma Antibody, LL2*, 32 Molecular Immunology 1413–27 (1995).

Claims 9 and 10 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg in view of Abrams, Allen, and Hansen[8] (*id.* at 4).

Claims 20 and 41 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg in view of Abrams, Allen, and Sakaguchi[9] (*id.*).

Claims 21 and 42 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg in view of Abrams, Allen, and Charlotte[10] (*id.*).

Claims 24–28 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg in view of Abrams, Allen, and Root[11] (*id.* at 4–5).

Claims 45 and 46 stand rejected under 35 U.S.C. § 103(a) as obvious over Goldenberg in view of Abrams, Allen, and Nepom[12] (*id.* at 5).

The Examiner relies on Goldenberg for teaching "a method for treating autoimmune disorders by administering antibodies that bind to a B cell antigen, such as the CD22 antigen, conjugated to a drug" (Ans. 4). The Examiner finds that Goldenberg teaches "that anti-B cell antibodies suitable for use in the invention may be an LL2 antibody" and "that SLE is among the autoimmune disorders that can be treated by the disclosed therapeutic composition" (*id.*). However, the Examiner finds that Goldenberg does "not

---

[8] Hansen et al., US 2003/0219433 A1, Nov. 27, 2003.
[9] Nahoko Sakaguchi et al., *Reactive Oxygen Species and Intracellular Ca^{2+}, Common Signals for Apoptosis Induced by Gallic Acid*, 55 Biochemical Pharmacology 1973–81 (1998).
[10] Charlotte Magdelaine-Beuzelin et al., *IgG1 Heavy Chain-Coding Gene Polymorphism (G1m Allotypes) and Development of Antibodies-to-Infliximab*, 19 Pharmacogenetics & Genomics 383–87 (2009).
[11] Root et al., US 4,200,690, Apr. 29, 1980.
[12] Gerald T. Nepom, *Therapy of Autoimmune Diseases: Clinical Trials & New Biologics*, 14 Current Opinion Immunology 812–15 (2002).

teach that an antibody and therapeutic agent can be conjugated via a linker, nor . . . the camptothecin, SN-38, as a therapeutic agent" (*id.* at 5).

The Examiner relies on Abrams for teaching "that for some immunoconjugates that comprise antibodies linked to therapeutic compounds, the biological activity of the compound may be reduced if the compound is attached to the antibody" and that, "[t]herefore, immunoconjugates comprising linkages which are cleavable in the vicinity of the target site may be used" (*id.*). In view of Abrams, the Examiner concludes that it would have been obvious "to prepare [Goldenberg's] immunoconjugates comprising an antibody and a therapeutic agent that are conjugated via a linker" (*id.* at 6).

The Examiner relies on Allen for teaching "that the camptothecin analogue SN-38 is a cytotoxic agent that has a deleterious or toxic effect on cells" (*id.* at 5). The Examiner concludes:

> One of ordinary skill in the art would have been motivated to arrive at the claimed invention, because by administering an immunoconjugate consisting of an anti-CD22 antibody conjugated to SN-38 to patients with SLE, said immuno-conjugate would bring B cells responsible for producing autoantibodies into contact with SN-38, and the SN-38 would be expected to have a deleterious or toxic effect on the autoantibody-producing B cells.

(*Id.* at 6.)

ISSUE

Appellants traverse the rejection over Goldenberg in view of Abrams and Allen (App. Br. 3–16). With regard to the other obviousness rejections, Appellants merely argue that the additionally applied references do not overcome the deficiencies of Goldenberg, Abrams, and Allen (*id.* at 16–18).

Thus, the following issue is dispositive for all of the rejections on appeal: Does the evidence supports the Examiner's conclusion that the combination of Goldenberg, Abrams, and Allen suggest the method of representative claim 1?

ANALYSIS

Goldenberg states that "[a]utoimmune diseases are a class of diseases associated with a B-cell disorder" and that the "most common treatments are corticosteroids and cytotoxic drugs" (Goldenberg 2: 6–10). Goldenberg "relates to immunotherapeutic methods for treating autoimmune disorders . . . by administering antibodies that bind to a B-cell antigen, such as the CD22 . . . antigen" (*id.* at 1: 11–14). Goldenberg discloses that the antibodies "may be naked or conjugated to a drug, toxin or therapeutic radioisotope" (*id.* at 1: 15–16). Goldenberg also discloses that "[d]rugs which are known to act on B-cells, plasma cells and/or T-cells are particularly useful in accordance with the present invention, whether conjugated to a B-cell antibody, or administered as a separate component in combination with a naked or conjugated B-cell antibody" (*id.* at 16: 31 to 17: 2).

Abrams discloses that a "problem associated with some methods of linking certain therapeutic compounds to antibodies is that the biological activity of the compound (e.g., drug, toxin, etc.) may be reduced when the compound is attached to the antibody" (Abrams, col. 6, ll. 55–59). Abrams therefore discloses "immunoconjugates comprising linkages which are cleavable in the vicinity of the target site" (*id.* at col. 6, ll. 63–65).

Allen discloses that cytotoxic agents include "a topoisomerase I inhibitor, such as camptothecin and its analogues, including SN-38" (Allen, col. 8, ll. 50–52). In view of the teachings of Goldenberg, Abrams, and Allen, we conclude that the Examiner has set forth a prima facie case of obviousness (Ans. 4–6).

Appellants argue, however, that it "would not have been *prima facie* obvious to conjugate a camptothecin such as SN-38 to an antibody for delivery" (App. Br. 6). In particular, Appellants argue:

> The fact that techniques in which SN-38 and other camptothecin derivatives are formulated attached to delivery agents such as polymers, polymeric micelles, or liposomes as carriers failed to show antitumor activity in clinical studies contravenes any conclusion by the examiner that it would have been obvious to attach SN-39 [sic, SN-38] to an antibody for delivery.

(*Id.* at 7 (emphasis omitted).) We are not persuaded.

Appellants have submitted a Declaration of one of the inventors, Dr. Goldenberg,[13] which states:

> Several approaches have been reported making use of polymers, polymeric micelles, or liposomes as carriers of SN-38 and other camptothecin derivatives for protracted release of the active drug or for passive targeting to tumor sites. So far, those conjugated with SN-38, such as polyethylene glycol (PEG), have failed to show antitumor activity in clinical studies.

(Decl. ¶ 5.) However, we do not agree with Appellants that this statement suggests that the claimed conjugate would not have been expected to work. In fact, the Declaration states, based on the above-mentioned failure, that

---

[13] Declaration under 37 C.F.R § 1.132 of Dr. David M. Goldenberg, signed September 23, 2014 (filed September 29, 2014).

"targeting by attachment to an anticancer antibody appears to be a preferred approach" (*id.*).

Appellants also argue that "there is data of record showing that the results for ADCs [(antibody-drug conjugates)] comprising SN-38 are unexpected as compared to results with unconjugated irinotecan," which is the parent of SN-38 (App. Br. 7–8 & 10). In support of this position, Appellants point to the Goldenberg Declaration, as well as Examples 14 and 15 of the present Specification and Sharkey[14] (*id.* at 9). We are not persuaded.

Sharkey discloses "the efficacy of SN-38 conjugates prepared with epratuzumab [(Emab)] . . . , humanized anti-CD22 . . . , was examined for the treatment of B-cell malignancies" (Sharkey, Abstract). Sharkey also discloses that "Emab--SN-38 is active in lymphoma and leukemia at doses well below toxic levels" (*id.*). In addition, Sharkey discloses that "[c]ross-linked, unconjugated epratuzumab had no effect on cell viability, but Emab–SN-38 killed 100% of the cells at approximately 1 to 10 nmol/L" (*id.* at 226). Similarly, the Specification states that "[h]umanized anti-CD22 MAb (epratuzumab) conjugated with SN-38 . . . shows potent efficacy for therapy of hematologic tumors" (Spec. 87).

The Declaration states that it "is surprising . . . that conjugation of Emab to SN-38 does not increase the toxicity, since it has a different detoxification mechanism, with reduced production of glucuronidated

---

[14] Robert M. Sharkey et al., *Epratuzumab–SN-38: A New Antibody-Drug Conjugate for the Therapy of Hematologic Malignancies*, 11 Molecular Cancer Therapeutics 224–34 (2011).

SN-38, thus mitigating side effects, such as neutropenia and diarrhea, usually associated with SN-38 released from irinotecan or Camptosar" (Decl. ¶ 11). The Declaration also states that it "was completely unexpected that the negative side effects of the camptothecins could be mitigated by administering them as a conjugate, and that a much lower dose of the camptothecin could be administered without loss of efficacy" (*id.* ¶ 13).

However, as noted by the Examiner (Ans. 22), "[t]umor-directed therapy has the potential to improve efficacy, by increasing the intratumoral concentration of the targeted agent, and to minimize toxicity by reducing systemic exposure" (Trail[15] 584). Thus, we agree with the Examiner that Appellants have not adequately explained why

> the invention of Goldenberg et al. would [not] be expected to more effectively deliver a therapeutic agent, such as a camptothecin, to a CD22-expressing autoimmune cell when compared to the delivery of an unconjugated camptothecin, because the conjugate of Goldenberg et al. would be expected to deliver a therapeutic agent directly to the cells that are mediating autoimmune disease.

(Ans. 18.)

We note Appellants' arguments that "even [cancer] patients who had failed prior therapy with irinotecan or Camptosar, both topoisomerase-1 inhibitors, responded to IMMU-132," which targets the TROP-2 antigen, and that

> since many of the patients had failed therapy with unconjugated irinotecan, it is entirely unexpected that the approach of

---

[15] Pamela A. Trail & Albert B. Bianchi, *Monoclonal Antibody Drug Conjugates in the Treatment of Cancer*, 11 Current Opinion Immunology 584–88 (1999).

> conjugating to an antibody would have led to any response at all, and certainly not to a disease control rate of 82%, which included patients for whom irinotecan or Camptosar was not efficacious!

(App. Br. 7–8 (emphasis omitted); *see also* Decl. ¶ 8.)

However, we agree with the Examiner that Appellants have not adequately explained why this data is sufficient to demonstrate unexpected results for the use of an *anti-CD22* antibody drug conjugate in the treatment of an *autoimmune disease* (Ans. 26 ("Appellant[s'] allegedly unexpected results, which are concerned with treating solid tumors, do not predict the efficacy of treating a B cell-mediated autoimmune disease with an anti-CD22/camptothecin conjugate.")). In addition, we note that Appellants' data does not provide a comparison to the closest prior art, which teaches the use of an anti-CD22 antibody drug conjugate in the treatment of an autoimmune disease.

In this regard, we recognize that the Declaration states that, "since CD22+ B cells are a proven therapeutic target for the therapy of autoimmune diseases (as evidenced by published results of epratuzumab in patients with moderate/severe systemic lupus erythematosus and Sjögren's disease), [Dr. Goldenberg] find[s] these data persuasive of success in treating autoimmune disease" (Decl. ¶ 12). However, we do not agree with Appellants that evidence of an expectation of success is sufficient to demonstrate unexpected results.

In addition, we understand Appellants' position that reduced side effects "would not turn on the difference in the target cells, i.e., tumor versus autoimmune," and "[t]herefore the results with tumors can be extended to autoimmune disease" (App. Br. 12). However, this reasoning would not

apply to the data demonstrating efficacy. Additionally, we conclude that Appellants have not clearly pointed to sufficient data to support the position that the claimed method provides unexpectedly reduced side effects.

We also note that the issue to be decided by the Board is not "whether an overall disease control rate of 82% with an SN-38 conjugate, in a study where 8 out of 22 patients had failed prior therapies with irinotecan or Camptosar, is 'expected.'" (*Id.* at 8.) Instead, given that Appellants have the burden of demonstrating unexpected results, the issue is whether Appellants have sufficiently demonstrated that the results are unexpected and relevant to the present claims, which recite the use of an anti-CD22 antibody drug conjugate in a method of treating an autoimmune disease. We conclude that they have not.

Appellants also argue that the "fact that the SN-38 from the ADC concentrates 120-fold over that from irinotecan is a result that could not have been predicted by the skilled artisan" (*id.* at 9). We are not persuaded.

The Declaration does state that "studies clearly show that the SN-38 derived from the ADC concentrates by a factor of about 120-fold over that derived from irinotecan, proving the selectively increased delivery of the cytotoxic drug, SN-38, by the ADC without increasing host toxicity" and that the "improved therapeutic index is also confirmed in the clinical experience, where repeated cycles of 8-10 mg/kg given on days 1 and 8 of a 21-day therapy cycle have shown objective antitumor responses in patients with advanced, relapsed/refractory cancers" (Decl. ¶ 11). However, it is not clear that these studies are relevant to claims directed to the use of an *anti-CD22* antibody drug conjugate in the treatment of an *autoimmune disease*

and, even if we assume that they are, Appellants have not presented the underlying data that supports these conclusory statements, nor have they provided sufficient evidence that the selectivity and improved therapeutic index would have been unexpected in view of Goldenberg.

We note Appellants' argument that "'the magnitude of the therapeutic effect achieved by conjugation is *entirely unexpected.*' Two logs *in vitro* and 120-fold in the clinic, are certainly not modest or expected results." (Reply Br. 5.) However, "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

In addition, Appellants argue that they have "provided additional publications showing unexpected results achieved when anti-CD22 antibodies are used to treat autoimmune diseases" (App. Br. 13). We are not persuaded.

Appellants have pointed to several references (*id.* at 13–14). However, we agree with the Examiner that Appellants have not adequately explained how these references demonstrate that the claimed method provides an unexpectedly superior result (Ans. 26–27).

Appellants also argue that "Cardillo *et al.*[16] and Govindan *et al.*[17] counter the examiner's conclusion that a skilled artisan can expect and/or

---

[16] Thomas M. Cardillo et al., *Humanized Anti-Trop-2 IgG-SN-38 Conjugate for Effective Treatment of Diverse Epithelial Cancers: Preclinical Studies in Human Cancer Xenograft Models and Monkeys*, 17 Clinical Cancer Res. 3157–69 (2011).

[17] Serengulam V. Govindan et al., *Milatuzumab–SN-38 Conjugates for the Treatment of CD74$^+$ Cancers*, 12 Molecular Cancer Therapeutics 968–78 (2013).

predict the effect of administering any ADC" (Reply Br. 3). We are not persuaded.

As noted by Appellants (*id.* at 2–3), Cardillo teaches:

> We reported the preparation of antibody--drug conjugates (ADC) using an anti-CEACAM5 (CD66e) IgG coupled to several derivatives of SN-38, a topoisomerase-1 inhibitor that is the active component of irinotecan, or CPT-11 . . . . The derivatives varied in their *in vitro* serum stability properties, and *in vivo* studies found 1 form (designated CL2) to be more effective in preventing or arresting the growth of human colonic and pancreatic cancer xenografts than other linkages with more or less stability. Importantly, these effects occurred at nontoxic doses, with initial testing failing to determine a dose-limiting toxicity . . . . These results were encouraging, but also surprising, because the CEACAM5 antibody does not internalize, a property thought to be critical to the success of an ADC. We speculated that the therapeutic activity of the anti-CEACAM5-SN-38 conjugate might be related to the slow release of SN-38 within the tumor after the antibody localized.

(Cardillo 3157–58.) However, as with the data discussed above, this teaching does not relate to an anti-CD22 antibody or the treatment of an autoimmune disease. In addition, Cardillo states that the results were "surprising[] because the CEACAM5 antibody does not internalize" (*id.* at 3158). Appellants have not adequately explained how this would be relevant to the present claims.

As also noted by Appellants (Reply Br. 3), Govindan teaches that "[p]rior studies indicated a preference for a linker (CL2A) that allowed SN-38 to dissociate from the conjugate in serum with a half-life of approximately 1 day, rather than other linkers that were either more or less stable in serum" (Govindan 969). Govindan also teaches:

> When the CL2E-linked conjugate was found to be much less potent in the solid tumor cell lines than the CL2A conjugate, this suggested that the lower surface expression of CD74 on the solid tumor cell lines reduced the internalization of SN-38 via milatuzumab binding. However, when *in vivo* studies in Raji also showed the milatuzumab-CL2A-SN-38 was superior to the CL2E conjugate, other factors had to be affecting CL2E-based conjugate's efficacy.

(*Id.* at 976.) However, the present claims are not directed to a particular linker. Thus, it is not clear how Govindan demonstrates that the present claims provide an unexpectedly superior property. In particular, we do not agree with Appellants' implication that the inventors' "surprise" over various results is sufficient to demonstrate that the present method provides an unexpectedly superior result.

CONCLUSION

The evidence supports the Examiner's conclusion that the combination of Goldenberg, Abrams, and Allen suggest the method of representative claim 1. We therefore affirm the obviousness rejection over Goldenberg, Abrams, and Allen of claim 1. Claims 5–8, 15, 16, 18, 19, 22, 23, 29, 33, 36, 37, 39, 40, 43, and 44 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

Because they are not separately argued, we also affirm the obviousness rejections of: claims 2 and 30 over Goldenberg in view of Abrams, Allen, and Leung; claims 9 and 10 over Goldenberg in view of Abrams, Allen, and Hansen; claims 20 and 41 over Goldenberg in view of Abrams, Allen, and Sakaguchi; claims 21 and 42 over Goldenberg in view of Abrams, Allen, and Charlotte; claims 24–28 over Goldenberg in view of

Abrams, Allen, and Root; and claims 45 and 46 over Goldenberg in view of Abrams, Allen, and Nepom.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED